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# Neutrophil-to-lymphocyte and aspartate-to-alanine aminotransferase ratios predict hepatocellular carcinoma prognosis after transarterial embolization

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**Abstract**

The neutrophil-to-lymphocyte ratio (NLR) reflects the systematic inflammatory status, and the aspartate aminotransferase-to-alanine aminotransferase ratio (AAR) is a biomarker of liver fibrosis and cirrhosis. These values can be conveniently obtained from routine blood tests; however, their combined clinical utility has not been extensively studied in patients with hepatocellular carcinoma (HCC) undergoing transarterial chemoembolization (TACE). This study aimed to investigate the prognostic value of NLR-AAR in patients with unresectable HCC undergoing TACE. Data for 760 patients with newly diagnosed HCC were retrospectively evaluated. The NLR-AAR was calculated as follows: patients in whom both the NLR and AAR were elevated according to the receiver operating characteristic (ROC) curve analysis were assigned a score of 2; patients showing an elevation in one or neither of these indicators were assigned a score of 1 or 0, respectively. Univariate and multivariate analyses were performed to identify the clinicopathological variables associated with overall survival. An ROC curve was also generated and the area under the curve (AUC) was calculated to evaluate the discriminatory ability of each index at 1, 3, and 5 years of follow-up, as well as overall. The NLR-AAR consistently had a greater AUC value at 1 year (0.669), 3 years (0.667), and 5 years (0.671) post-TACE compared with either NLR or AAR alone. The median survival times of patients with a NLR-AAR of 0, 1, and 2 were 31.0 (95% confidence interval [CI] 24.0–38.0), 15.0 (95% CI 11.2–18.8), and 5.0 (95% CI 4.0–5.9) months, respectively ($P < .001$). Multivariate analysis showed that the NLR-AAR, elevated total bilirubin level, and vascular invasion were independently associated with overall survival. NLR and AAR, when combined to produce an inflammation-based index and fibrosis score, is an independent marker of poor prognosis in patients with HCC receiving TACE.

**Abbreviations:** AAR = aspartate aminotransferase-to-alanine aminotransferase ratio, AFP = alpha-fetoprotein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, AUC = area under the curve, AUROC = The area under the receiver operating characteristic, BCLC = Barcelona Clinic Liver Cancer classification, CI = confidence interval, CT = computed tomography, HCC = hepatocellular carcinoma, MELD = The model of end-stage liver disease, NLR = neutrophil-to-lymphocyte ratio, OS = overall survival, ROC = receiver operating characteristic, TACE = transarterial chemoembolization.

**Keywords:** aspartate aminotransferase-to-alanine aminotransferase ratio, hepatocellular carcinoma, neutrophil-to-lymphocyte ratio, prognosis, sensitivity and specificity, transarterial embolization

## 1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer[1] and the fourth leading cause of cancer-related death in China.[2] In most cases, HCCs are not amenable to resection owing to the tumor size and location or liver dysfunction. A common obstacle in HCC therapy is that the HCCs almost always occur in chronically inflamed livers.[3] According to the Barcelona Clinic Liver Cancer classification (BCLC) stage, transarterial chemoembolization (TACE) is the recommended adjuvant therapy for intermediate HCC; however, TACE is also indicated in some cases of advanced HCC (BCLC C stage) with preserved hepatic function to prolong survival as well as in real clinical settings. The duration of overall survival (OS) predicted in these patients is often <5 years; therefore, it would be useful to identify novel biomarkers that may facilitate the prediction of outcomes and selection of patients who would most likely benefit from TACE.

After radical resection of HCC, prognosis depends on factors such as tumor size and differentiation, vascular invasion, and resection margin status. However, most of these factors are not

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applicable for patients treated with TACE. Therefore, there is a need to identify a potential prognostic indicator that could be detected before TACE. Hematological components of the systemic inflammatory response have been investigated together to establish an inflammation-based prognostic index to predict HCC survival. Elevated neutrophil-to-lymphocyte ratio (NLR) has been shown to predict unfavorable overall and postoperative survival in HCCs after both curative[4] and palliative treatment.[5] However, the prognostic value of NLR in HCC is considered to be inferior to that of other inflammation-based indices.[6,7]

It is well known that HCC develops as a consequence of hepatic fibrosis progression.[8] Histological staging of liver fibrosis is essential for chronic hepatitis B and chronic hepatitis C patients. Although liver biopsy remains the gold standard for assessing the degree of active hepatitis and hepatic fibrosis, the clinical application of biopsy is limited owing to its invasiveness and risk of complications.[9] Because of all of these aforementioned drawbacks, efforts have been focused on identifying alternative methods (including direct/indirect markers) to obtain information on liver histology during treatment that can ultimately replace liver biopsy. The aspartate aminotransferase (AST)-to-alanine aminotransferase (ALT) ratio (AAR) has been validated as an index for assessing hepatic fibrosis in chronic liver diseases including chronic hepatitis B[10] and chronic hepatitis C.[11] Giannini et al[12] suggested that AAR could be used to differentiate between cirrhosis and HCC with a sensitivity of 75.9% and specificity of 55.7%. A recent study claimed that AAR is independently associated with early recurrence of HCC.[13] As the fibrosis indices correlate with liver fibrosis, we presume that these indices might be closely related to HCC development. However, whether preoperative AAR can also serve as a biomarker that can predict outcomes in patients with HCC who undergo TACE remains unclear; in particular, the prognostic value of AAR in combination with NLR has not been determined.

To the best of our knowledge, no study has focused on the prognostic value of the combination of inflammatory and fibrosis indices in patients with unresectable HCC receiving TACE thus far. Therefore, this study aimed to clarify the prognostic value of AAR in HCC after TACE, and to demonstrate whether the prognostic accuracy is enhanced by the combination of NLR and AAR.

## 2. Methods

### 2.1. Ethics statement

Written informed consent was obtained from all patients prior to TACE. The study was approved by the independent ethics committees at the West China Hospital, Sichuan University. This study was conducted in accordance with the ethical standards of the World Medical Association Declaration of Helsinki.

### 2.2. Patients

Patients who received TACE as initial therapy for intermediate to advanced HCC from January 2007 to December 2013 at the Department of Liver Surgery, West China Hospital, Sichuan University were enrolled within a prospectively maintained database. All patients satisfied the diagnostic criteria for HCC based on radiologic or histologic grounds according to the American Association for the Study of the Liver guidelines.[14]

**Table 1**

**The combination of NLR and AAR as prognostic indices.**

| Variable | Score |
|---|---|
| NLR | |
| ≤2.2 | 0 |
| >2.2 | 1 |
| AAR | |
| ≤1.2 | 0 |
| >1.2 | 1 |
| NLR-AAR | |
| NLR=0 and AAR=0 | 0 |
| NLR=1 or AAR=1 | 1 |
| NLR=1 and AAR=1 | 2 |

AAR=aspartate transaminase-to-alanine transaminase ratio, NLR=neutrophil-to-lymphocyte ratio.

Eligibility for inclusion in the present study was defined using the following criteria: receiving TACE as initial and monotherapy; Child-Pugh liver function of A or B; follow-up period ≥1 month; and presence of unresectable HCC as determined via multidisciplinary consensus. Major vascular invasion and portal vein thrombosis in patients with preserved hepatic function are not considered absolute contraindications to TACE at our center. Routine assessment was performed within 7 days before the interventional procedure, which included a complete physical examination, hematologic and biochemistry profiles, abdominal ultrasound and computed tomography (CT) or magnetic resonance imaging, and chest radiography or CT. The model of end-stage liver disease (MELD) score was calculated logarithmically based on serum bilirubin, serum creatinine, and prothrombin time. Detected serum alpha-fetoprotein (AFP) values ranged from 0 to 1210 μg/L; all AFP values >1210 μg/L were recorded as 1210 μg/L in our study.

### 2.3. Defining the combined inflammation and fibrosis grade

The NLR was calculated by dividing the neutrophil count by the lymphocyte count.[4] The AAR was calculated as AST/ALT.[15] The optimal cutoff values of the laboratory parameters were determined using receiver operating characteristic (ROC) curve analyses, based on the most prominent point on the ROC curve for "sensitivity" and "1-specificity," respectively. Then, the ideal cutoff values were defined using the Youden index (maximum [sensitivity + specificity − 1]).[16] Thus, a new inflammation and fibrosis grade, the NLR-AAR score, was devised by combining the NLR with the AAR. The NLR-AAR value was calculated based on their cutoff values as follows: patients with both an elevated NLR and AAR was assigned a score of 2, patients showing either an elevated NLR or AAR were assigned a score of 1, and patients in whom neither NLR nor AAR was elevated were assigned a score of 0 (Table 1).

### 2.4. TACE procedure and follow-up

A uniform TACE procedure was performed for each patient by 2 different experienced interventional radiologists who had similar experience with and expertise in the management of HCC. The Seldinger technique was used to access the right femoral artery under local anesthesia. First, chemotherapeutic agents, 5-fluorouracil (800–1000 mg) and epirubicin (30–40 mg), were injected; the dose was calculated according to the body surface area.

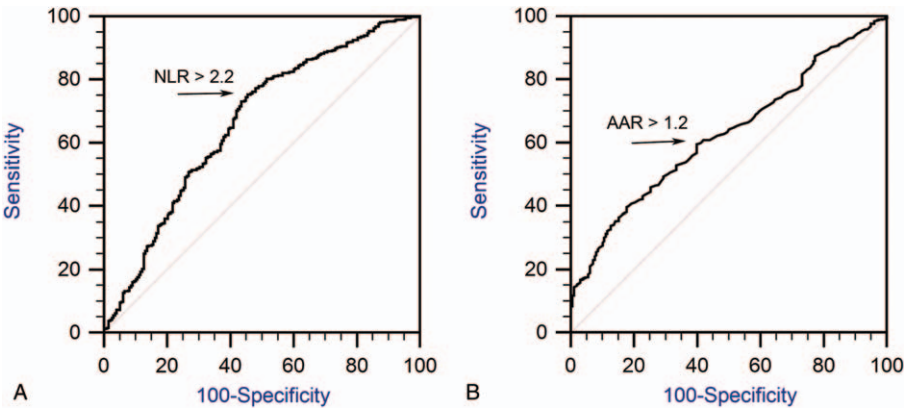


**Figure 1.** Receiver operating characteristics curves to assess the best cutoff value of neutrophil to lymphocyte ratio (NLR) and aspartate-to-alanine aminotransferase ratios (AAR). (A) ROC curve of NLR. AUROC: 0.664; 95% CI: 0.630–0.698; $P < .001$, with a sensitivity of 0.752 and specificity of 0.545. (B) ROC curve of AAR, AUROC: 0.625; 95% CI: 0.590–0.660; $P < .001$), with a sensitivity of 0.582 and specificity of 0.601.

Subsequently, ethiodized oil and polyvinyl alcohol were administered as embolic material until arterial stasis was achieved. TACE was undertaken via a lobar or sublobar approach, depending on the size, location, and arterial supply of the tumor.

One month after TACE, tumor responses were evaluated via routine blood tests, measurement of AFP levels, liver and kidney function, and contrast-enhanced CT. If elevated tumor markers (AFP), low lipiodol uptake, enlarged lesions, or new nodules were observed, the patients were readmitted for angiography and treatment after an interval of 1.5 to 3.0 months. Treatment was terminated if a patient could not tolerate the procedure because of a decline in his/her clinical status or if a patient presented a complete response. All patients were followed up until death or the cutoff date (December 31, 2013). Death within 30 days of the procedure was defined as periprocedural mortality, and these cases were excluded from the post-TACE survival analysis.

### 2.5. Statistics

Data are presented as the mean ± standard deviation, and categorical data are shown as frequencies and proportions. Categorical data are presented as frequencies and were analyzed using the Pearson $\chi^2$ test or Fisher exact test. The area under the receiver operating characteristic (AUROC) curve of the NLR and AAR indices was calculated to predict HCC survival. The Youden index was calculated to select the optimal cutoff value for stratifying patients with a high risk for cancer-related mortality. A univariate analysis was performed to assess the significance of the differences in the clinical or radiological data. A multivariate analysis was performed using the Cox regression model for variables with a significant difference in the univariate analysis. The associated 95% confidence interval (CI) was calculated. The OS was analyzed using the Kaplan-Meier method, and the equivalences of the survival curves were tested using log-rank statistics. An ROC curve was also generated and the AUC was calculated to evaluate the discriminatory ability of each index at 1, 3, and 5 years of follow-up, as well as overall. The z-statistic was used to compare the AUROC curves of the inflammation and fibrosis indices. For all the other statistical tests, a $P$ value $<.05$ was considered to be significant. All analyses were performed by using the IBM SPSS software package v.24.0 (IBM SPSS Inc, Chicago, IL), and all graphs were created using MedCalc v. 13.3.0.0 (MedCalc Software, Mariakerke, Belgium).

## 3. Results

### 3.1. Optimal cutoff values for the NLR and AAR

Using 5-year overall survival rate as an endpoint, we stratified each prognostic index according to the maximum joint sensitivity and specificity values based on the peak and cutoff points of the ROC curve. The optimal cutoff value for NLR was 2.2, with a sensitivity of 0.752 and specificity of 0.545 (AUROC curve: 0.664; 95% CI: 0.630–0.698; $P < .001$) (Fig. 1A). The optimal cutoff value for AAR was 1.2 with a sensitivity of 0.582 and specificity of 0.601 (AUROC curve: 0.625; 95% CI: 0.590–0.660; $P < .001$) (Fig. 1B). Accordingly, the patients were divided into 3 groups: NLR-AAR 0, NLR-AAR 1, and NLR-AAR 2.

### 3.2. Baseline characteristics

Overall, 760 patients underwent TACE as initial treatment for HCC including 643 male patients (84.6%) and 117 female patients (15.4%). Their median age was 56.5 (range, 19–89 years), and most patients (n = 649, 85.4%) had hepatitis B viral infection. The median Child-Pugh score was 6 (range, 5–9), with most cases classified as Child-Pugh A (n = 621, 81.7%). In total, 53.6% of the patients underwent >1 TACE session (range 1–9), and 447 patients (58.8%) had multiple tumor masses. Median tumor size was 7.6 cm (range 1.0–30.5 cm; largest diameter), and 409 (53.8%) patients had vascular invasion (including the portal and hepatic veins).

### 3.3. Associations between NLR-AAR grade and clinicopathologic characteristics of HCC patients

Among the 760 patients, 139 (18.3%) were classified as having a NLR-AAR score of 0, whereas 314 (41.3%) and 307 (40.4%) were classified as having a NLR-AAR score of 1 and 2, respectively. Patients in the NLR-AAR 2 group had relatively higher AST, ALT, total bilirubin, and AFP levels; higher Child-Pugh scores; and larger tumor sizes than patients in the other groups ($P < .05$). In contrast, the albumin level was significantly lower in patients with an NLR-AAR score of 2 than in the other groups ($P < .05$). An elevated NLR-AAR score was associated with multiple nodules and vascular invasion. The demographic and clinicopathologic features of patients according to NLR-AAR score are shown in Table 2.

**Table 2**

**Comparison of the clinical characteristics of patients with different NLR-AAR grades.**

| Variable | NLR-AAR 0 (n = 139) | NLR-AAR 1 (n = 314) | NLR-AAR 2 (n = 307) | *P* value |
|---|---|---|---|---|
| Age, y | 54.1 ± 13.8 | 55.7 ± 13.1 | 55.4 ± 13.6 | .505 |
| Gender (male/female) | 123/16 | 267/47 | 254/54 | .248 |
| BMI, kg/m$^2$ | 23.1 ± 3.2 | 22.6 ± 2.9 | 22.2 ± 3.2 | .145 |
| HBsAg (positive/negative) | 125/14 | 263/51 | 261/46 | .223 |
| ALT, IU/L | 69.9 ± 67.2 | 69.2 ± 65.9 | 43.7 ± 31.5 | <.001* |
| AST, IU/L | 55.3 ± 34.8 | 71.6 ± 64.1 | 92.8 ± 76.8 | <.001* |
| TBIL, μmol/L | 18.2 ± 14.9 | 19.3 ± 13.3 | 24.7 ± 33.1 | .004* |
| ALB, g/L | 40.7 ± 6.1 | 39.4 ± 5.8 | 37.1 ± 6.1 | <.001* |
| Neutrophil count ($\times 10^9$ L$^{-1}$) | 2.7 ± 1.0 | 3.9 ± 2.2 | 4.6 ± 2.7 | <.001† |
| Lymphocyte count ($\times 10^9$ L$^{-1}$) | 1.7 ± 0.6 | 1.3 ± 0.5 | 1.0 ± 0.4 | <.001† |
| PT, s | 12.2 ± 1.2 | 12.5 ± 1.5 | 12.8 ± 2.0 | <.001* |
| Creatinine, μmol/L | 76.1 ± 17.5 | 80.3 ± 63.3 | 74.0 ± 20.2 | .2 |
| Child-Pugh score | 5.4 ± 0.7 | 5.5 ± 0.9 | 6.0 ± 1.1 | <.001* |
| MELD score | 5.6 ± 6.7 | 5.8 ± 3.6 | 6.2 ± 3.8 | .304 |
| AFP, μg/L | 424.6 ± 524.0 | 470.3 ± 547.2 | 616.9 ± 559.1 | <.001* |
| Largest tumor size, cm | 5.9 ± 3.0 | 7.2 ± 4.0 | 9.5 ± 4.6 | <.001* |
| Tumor number (single/multiple) | 76/63 | 147/167 | 90/217 | <.001† |
| Vascular invasion (absent/present) | 88/51 | 148/166 | 115/192 | <.001† |

AAR = aspartate aminotransferase-to-alanine aminotransferase ratio, AFP = α-fetoprotein, ALB = albumin, ALT = alanine transaminase, AST = aspartate transaminase, HBsAg = hepatitis B surface antigen, NLR = neutrophil-to-lymphocyte ratio, PLT = platelets, PT = prothrombin time, TBI = total bilirubin, WBC = white blood cells.

* $P < .05$ for NLR-AAR 2 versus the other 2 groups.

† $P < .05$ each group compared with each other.

### 3.4. Survival analysis

A total of 562 patients (73.9%) died during the follow-up period. The median survival duration was 12 months (range, 1–69 months). The 1-, 3-, and 5-year OS rates were 49.6%, 25.0%, and 12.1%, respectively (Fig. 2A). The 760 HCC patients were divided into 2 groups according to their NLR: ≤2.2 (n = 238) and >2.2 (n = 522). Using the Kaplan-Meier method to analyze patient survival, we found that the median OS for patients with an NLR ≤2.2 was 27 months (95% CI, 21.3–32.7 months) compared with 7 months (95% CI, 5.7–8.3 months) for those with an NLR >2.2. However, the 1-, 3- and 5-year OS rates of patients with an NLR ≤2.2 were significantly higher than those of patients with an NLR >2.2 (70.5%, 39.9%, and 27.4% vs 40.2%, 18.2%, and 6.8%, respectively, $P < .001$) (Fig. 2B). Our findings therefore indicated that high NLRs are correlated with a low survival rate in patients with unresectable HCC.

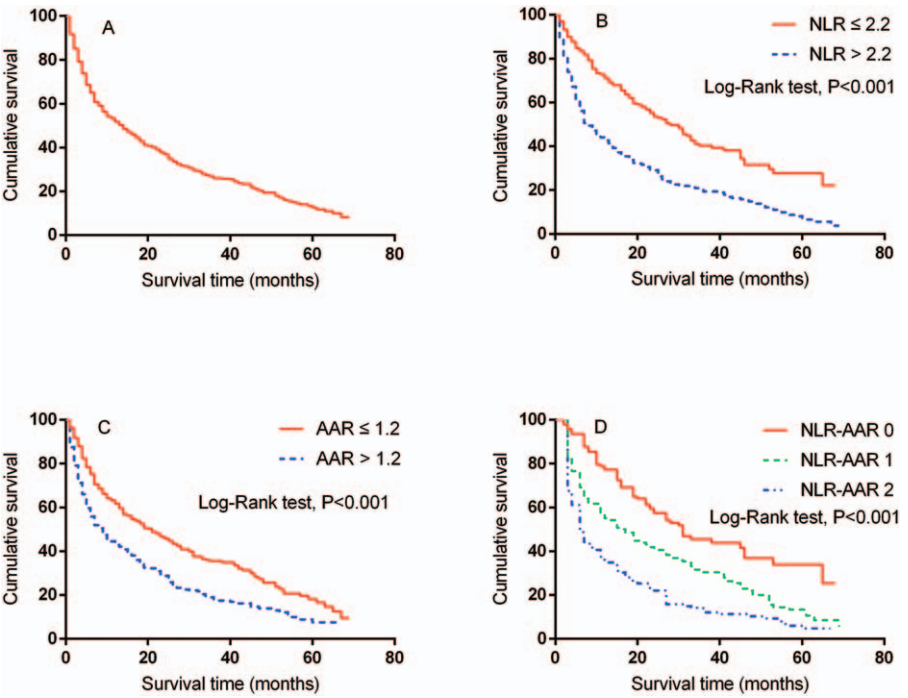


**Figure 2.** Kaplan-Meier survival curves for overall survival in HCC patients undergoing transarterial chemoembolization for hepatocellular carcinoma. (A) Overall survival; (B) NLR; (C) AAR; and (D) NLR-AAR.

**Table 3**

**Prognostic factors associated with OS.**

| Variables | Univariate | | Multivariate | |
|---|---|---|---|---|
| | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| Age, y (≤55, >55) | 0.924 (0.782–1.092) | .354 | | |
| Gender (male/female) | 1.113 (0.898–1.429) | .291 | | |
| HBsAg (positive/negative) | 0.978 (0.779–1.227) | .845 | | |
| ALB, g/L (≤35, >35) | 0.710 (0.590–0.853) | <.001 | | |
| TBIL, μmol/L (≤28, >28) | 1.647 (1.334–2.034) | <.001 | 1.718 (1.123–2.628) | .013 |
| ALT, IU/L (≤40, >40) | 1.355 (1.145–1.603) | <.001 | | |
| AST, IU/L (≤35, >35) | 2.029 (1.651–2.492) | <.001 | | |
| PT, s (≤12/>12) | 1.136 (0.957–1.349) | .146 | | |
| AFP, ng/mL (≤400/>400) | 1.601 (1.355–1.891) | <.001 | | |
| Child-Pugh grade (A/B) | 1.337 (1.084–1.649) | .007 | | |
| MELD score (≤10/>10) | 1.445 (1.096–1.940) | .009 | | |
| Largest tumor size, cm (≤10/>10) | 1.739 (1.391–2.171) | <.001 | | |
| Tumor number (single/multiple) | 1.021 (0.840–1.242) | .831 | | |
| Vascular invasion (present/absent) | 2.002 (1.594–2.515) | <.001 | 1.690 (1.268–2.253) | <.001 |
| BCLC (B/C stage) | 2.188 (1.745–2.743) | <.001 | | |
| NLR (≤2.2, >2.2) | 2.144 (1.764–2.606) | <.001 | | |
| AAR (≤1.2, >1.2) | 1.664 (1.406–1.969) | <.001 | | |
| NLR-AAR score | | | | |
| 0 | | | | |
| 1 | 1.737 (1.332–2.266) | <.001 | 1.945 (1.516–3.121) | .006 |
| 2 | 3.054 (2.349–3.970) | <.001 | 3.510 (1.800–6.846) | <.001 |

AAR = aspartate aminotransferase-to-alanine aminotransferase ratio, AFP = α-fetoprotein, ALB = albumin, ALT = alanine transaminase, AST = aspartate transaminase, BCLC = Barcelona Clinic Liver Cancer, MELD = Model for End-stage Liver Disease, NLR = neutrophil-to-lymphocyte ratio, PT = prothrombin time, TBIL = total bilirubin.

Likewise, the HCC patients were divided into 2 groups according to their AAR profiles: AAR ≤1.2 (n = 354) and AAR >1.2 (n = 406). The median OS for patients with an AAR ≤1.2 was significantly higher than that for patients with an AAR >1.2 (19 months, 95% CI, 14.0–23.9 months vs 7 months, 95% CI, 5.3–8.7 months, respectively, $P < .001$). In addition, the 1-, 3- and 5- year OS rates for patients with an AAR ≤1.2 were significantly higher than those for patients with an AAR >1.2 (60.3%, 34.7%, and 17.8% vs 40.3%, 16.5%, and 7.1%, respectively, $P < .001$) (Fig. 2C). A high AAR therefore implied poor OS in HCC patients undergoing TACE.

Finally, patients with NLR-AAR scores of 0 had the most favorable outcomes, with a median OS of 31 months (95% CI, 24.0–38.0 months) compared with patients in the NLR-AAR 1 category (median OS, 15 months; 95% CI, 11.2–18.8 months) and the NLR-AAR 2 category (median OS, 5 months; 95% CI, 4.0–5.9 months). The 1-, 3-, and 5-year survival rates were 76.1%, 44.8%, and 33.3% for patients in the NLR-AAR 0 category; 54.1%, 29.8%, and 11.9% for those in the NLR-AAR 1 category; and 34.5%, 11.1%, and 4.4% for those in the NLR-AAR 2 category, respectively ($P < .05$) (Fig. 2D). Therefore, the findings indicate that preoperative NLR-AAR scores of 1 or 2 were correlated with poor survival.

### 3.5. Risk factors for outcome after TACE

The results of the univariate and multivariate analyses of the predictors of postoperative OS are shown in Table 3. Preoperative AST ($P < .001$), ALT ($P < .001$), total bilirubin ($P < .001$), albumin ($P < .001$), AFP ($P < .001$), Child-Pugh grade ($P = .007$), Model for End-stage Liver Disease score ($P = .009$), BCLC stage ($P < .001$), vascular invasion ($P < .001$), tumor size ($P < .001$), NLR ($P < .001$), AAR ($P < .001$), and NLR-AAR grade ($P < .001$) were significantly associated with postoperative outcomes. Multivariate analysis confirmed that the following factors were independent predictors of OS: total bilirubin ($P = .013$; HR 1.718; 95% CI, 1.123–2.628), vascular invasion ($P < .001$; HR 1.690; 95% CI, 1.268–2.253), NLR-AAR score 1 ($P = .006$; HR 1.945; 95% CI, 1.516–3.121), and NLR-AAR score 2 ($P < .001$; HR 3.510; 95% CI, 1.800–6.846) (Table 3).

### 3.6. Discriminatory performance of NLR, AAR, and NLR-AAR

The prognostic value of each inflammation fibrosis index and score was compared by analyzing the AUC values. ROC curves were calculated based on the patients' survival status at the 1-, 3-, and 5-year follow-up session, as well as overall (Fig. 3). The NLR-AAR score had a superior discriminative capacity when compared with NLR and AAR individually, and consistently exhibited a higher AUC value than the other single indices (Table 4).

## 4. Discussion

Currently, TACE is the standard therapy for BCLC-B stage HCC patients.[17] Nevertheless, several BCLC-C stage HCC patients with compensatory hepatic function undergo TACE owing to its effects on prolonging survival and alleviating symptoms. The prognosis of patients with intermediate to advanced HCC varies widely because BCLC-B and C stage HCC comprises a heterogeneous patient population with a wide range of disease burdens. Therefore, we believe there is an urgent need to identify novel biomarkers to accurately predict the prognosis for patients with unresectable HCC undergoing TACE. In the present study, we confirmed that a combined inflammation- and fibrosis-based NLR-AAR score is an independent predictive factor for the prognosis of patients with intermediate to advanced HCC undergoing TACE. An NLR-AAR score of 2 was found to be correlated with obviously poor prognosis after TACE.

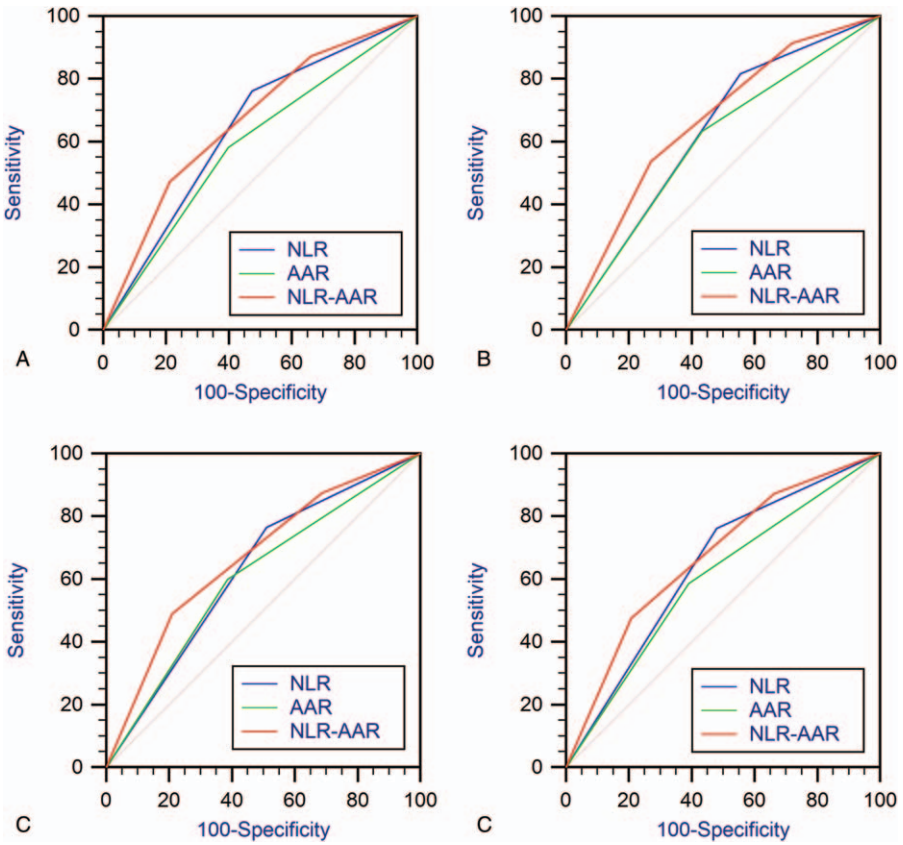


**Figure 3.** Comparisons of the area under the curve (AUC) for outcome prediction. Comparisons among the inflammation-based index and scores in patients after transarterial chemoembolization. (A) Overall survival time; (B) at 1 y; (C) at 3 y; and (D) at 5 y.

An increasing number of studies have examined the role of systemic inflammation-based biomarkers in tumor progression.[18,19] A previous study demonstrated that an elevated pretreatment NLR, a biomarker that is correlated with systemic inflammation and immune function, is a useful predictor of survival for patients with HCC treated with liver transplantation, hepatectomy, radiofrequency ablation, TACE, or sorafenib. Recently, a meta-analysis[19] validated the importance of NLR for

**Table 4**

**Comparison between the areas under the receiver operating characteristic curves of the inflammation-based indices and fibrosis grades.**

| Period | AUC (95% CI) | z-statistic | *P* value |
|---|---|---|---|
| Overall | | | |
| NLR | 0.643 (0.608–0.678) | 1.928 | .054* |
| AAR | 0.591 (0.556–0.627) | 5.291 | <.001† |
| NLR-AAR | 0.669 (0.634–0.702) | 1.655 | .098‡ |
| 1 y | | | |
| NLR | 0.631 (0.595–0.665) | 1.358 | .175* |
| AAR | 0.600 (0.564–0.635) | 5.633 | <.001† |
| NLR-AAR | 0.667 (0.632–0.700) | 2.666 | .008‡ |
| 3 y | | | |
| NLR | 0.627 (0.592–0.661) | 0.787 | .431* |
| AAR | 0.607 (0.571–0.642) | 4.609 | <.001† |
| NLR-AAR | 0.670 (0.635–0.704) | 2.919 | .004‡ |
| 5 y | | | |
| NLR | 0.641 (0.605–0.675) | 1.611 | .107* |
| AAR | 0.597 (0.562–0.633) | 5.113 | <.001† |
| NLR-AAR | 0.671 (0.637–0.705) | 2.023 | .043‡ |

AAR = aspartate aminotransferase-to-alanine aminotransferase ratio, AUC = area under the curve, AUROC = area under the receiver operating characteristics curve, CI = confidence interval, NLR = neutrophil-to-lymphocyte ratio.

* NLR compared with AAR.

† AAR compared with NLR-AAR.

‡ NLR compared with NLR-AAR.

assessing the overall survival and recurrence-free or disease-free survival of HCC patients, which was based on a relatively large amount of relevant data (38 articles for overall survival and 20 articles for recurrence-free or disease-free survival). Inflammation, especially local inflammation in the tumor microenvironment, is known to play a role in carcinogenesis and tumor progression. Motomura et al[20] demonstrated that vascular endothelial growth factor, interleukin-8, interleukin-17, CD68, and CD163 levels were similar between patients with high and low preoperative NLRs who underwent liver transplantation. They suggested that the ability of NLR to predict tumor recurrence may be brought about by the inflammatory tumor microenvironment. On the other hand, lymphocytes are important components of the adaptive immune system that provide a cellular basis for cancer immunosurveillance and immunoediting, and evidence has proven that the presence of infiltrating lymphocytes suggest the generation of an effective anti-tumor cellular immune response. In other words, a lower lymphocyte count might indicate an inadequate immunological antitumor response and a weakened defense against cancer, with a consequently poor prognosis.[21]

It is worth pointing out that the degree of liver fibrosis was confirmed as a negative predictor of liver regeneration and restoration of liver function after hepatectomy.[22] Previous studies have also reported that fibrosis is the main risk factor for postoperative complications, and advanced hepatic fibrosis or cirrhosis is closely associated with death and development of postoperative complications such as ascites, liver failure, and worsening encephalopathy.[23] Currently, measurement of hepatic stiffness using transient elastography is widely practiced in clinical trials because liver biopsy can thus be avoided in most patients. Nevertheless, hepatic stiffness is not routinely assessed in HCC patients before TACE owing to its high cost implications.[24] The AAR is a validated indicator of the histologic degree of liver fibrosis and cirrhosis. Although Wang et al[13] reported that AAR was independently associated with early recurrence of HCC, other studies claim that AAR yields a lower diagnostic performance in terms of detecting significant fibrosis when compared with other indices.[25] Our result confirmed the prognostic role of AAR in patients with unresectable HCC after TACE: patients with AAR $\leq$1.2 showed a much better post-TACE survival rate at 1, 3, and 5 years compared with those with AAR $>$1.2. Although the exact mechanisms by which a high AAR is associated with a poor outcome remains unknown, we offer the following potential explanations. Firstly, both AST and ALT are hepatocyte-predominant enzymes[26]; advanced liver disease is associated with mitochondrial injury, a feature that can substantially increase the release of AST. Moreover, elevation of AST with progression of liver fibrosis is caused by reduced AST clearance and mitochondrial injury with increased release of AST relative to ALT.[27] Moreover, serum AST/ALT level is associated with remnant liver inflammatory necrosis,[28] which facilitates the invasion and recurrence of HCC.[13]

Thus, with the advantages of being inexpensive and easily available, NLR and AAR have been extensively investigated and identified as independent prognostic factors in HCC patients, at least to a certain extent. However, because the predictive value of single factor alone is not adequate to achieve an accurate prediction of prognosis, prognostic scores that combine markers of inflammation and fibrosis, such as the NLR-AAR, are warranted. To the best of our knowledge, this is the first study to address the prognostic value of a combination of inflammation and fibrosis system-based prognostic factors in patients with HCC undergoing TACE. In our study, NLR-AAR yielded a higher prognostic accuracy than that achieved with either scale alone. The NLR-APRI showed the best discriminatory performance and consistently exhibited a higher AUC value at 1, 3, and 5 years post-TACE, as well as OS. Not surprisingly, the independent prognostic value of the NLR-AAR was strengthened by cross-validation, in which only the NLR-AAR was found to have an independent prognostic value in the multivariate analysis.

Moreover, relationships between clinicopathological features and the NLR-APRI grade were identified. We noted that the NLR-AAR correlated significantly with elevated liver functional reserve, larger tumor size, and the presence of vascular invasion, suggesting that a high NLR-AAR score correlates with a more aggressive HCC biological phenotype. Consequently, the combination of the NLR and AAR inevitably possesses both accurate and clinically meaningful prognostic value for intermediate to advance HCC patients undergoing TACE. It should also be mentioned that our results indicate that patients with an NLR-AAR score of 2 had generally poor prognoses after TACE, which may help clinicians predict the possibility of poor survival in patients with HCC after TACE and thus establish appropriate observations plan or explore other treatments. Meanwhile, the NLR-AAR is almost universally available and cost-effective for routine preoperative practices, making it a reasonable candidate for clinical application.

However, the results should be interpreted cautiously owing to some limitations of the study. First, the retrospective nature of the present study cannot be ignored, even with the application of strict inclusion and exclusion criteria to minimize the risk of potential biases. Second, the study population comprised primarily hepatitis B virus-related HCC cases that have been only internally validated. Therefore, a multicenter and potentially prospective cohort study with a large sample of patients is needed to verify the prognostic value of NLR-AAR in HCC, and the potential mechanism underlying this association.

In conclusion, the results of our single-center study verified that preoperative NLR-AAR grade could be a prognostic factor for predicting the prognosis of patients with intermediate to advanced HCC after TACE. The findings indicate that prognosis-related serum biomarkers in addition to traditional tumor clinicopathological features should be taken into account when formulating the treatment plan.

## References

[1] Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011;61:69–90.
[2] Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016;66:115–32.
[3] Eggert T, Greten TF. Current standard and future perspectives in non-surgical therapy for hepatocellular carcinoma. Digestion 2017;96:1–4.
[4] Xiao G. Neutrophil-lymphocyte ratio predicts the prognosis of patients with hepatocellular carcinoma after liver transplantation. World J Gastroenterol 2013;19:8398–407.
[5] Zhou D, Liang J, Xu L, et al. Derived neutrophil to lymphocyte ratio predicts prognosis for patients with HBV-associated hepatocellular carcinoma following transarterial chemoembolization. Oncol Lett 2016;11:2987–94.
[6] Kinoshita A, Onoda H, Imai N, et al. Comparison of the prognostic value of inflammation-based prognostic scores in patients with hepatocellular carcinoma. Br J Cancer 2012;107:988–93.
[7] He CB, Lin XJ. Inflammation scores predict the survival of patients with hepatocellular carcinoma who were treated with transarterial chemoembolization and recombinant human type-5 adenovirus H101. PloS One 2017;12:e174769.

[8] Liaw YF, Chu CM. Hepatitis B virus infection. Lancet 2009;373:582–92.
[9] Rockey DC, Bissell DM. Noninvasive measures of liver fibrosis. Hepatology 2006;43(suppl 1):S113–20.
[10] Williams AL, Hoofnagle JH. Ratio of serum aspartate to alanine aminotransferase in chronic hepatitis. Relationship to cirrhosis. Gastroenterology 1988;95:734–9.
[11] Giannini E, Botta F, Fasoli A, et al. Progressive liver functional impairment is associated with an increase in AST/ALT ratio. Dig Dis Sci 1999;44:1249–53.
[12] Giannini E, Risso D, Botta F, et al. Validity and clinical utility of the aspartate aminotransferase-alanine aminotransferase ratio in assessing disease severity and prognosis in patients with hepatitis C virus-related chronic liver disease. Arch Intern Med 2003;163:218–24.
[13] Wang ZX, Jiang CP, Cao Y, et al. Preoperative serum liver enzyme markers for predicting early recurrence after curative resection of hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int 2015;14: 178–85.
[14] Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology 2005;42:1208–36.
[15] Lin CS, Chang CS, Yang SS, et al. Retrospective evaluation of serum markers APRI and AST/ALT for assessing liver fibrosis and cirrhosis in chronic hepatitis B and C patients with hepatocellular carcinoma. Intern Med 2008;47:569–75.
[16] Youden WJ. Index for rating diagnostic tests. Cancer 1950;3:32–5.
[17] European Association for the Study of the Liver, European Organisation for Research and Treatment of CancerEASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908–43.
[18] Sun X, Shi X, Chen Y, et al. Elevated preoperative neutrophil-lymphocyte ratio is associated with poor prognosis in hepatocellular carcinoma patients treated with liver transplantation: a meta-analysis. Gastroenterol Res Pract 2016;2016:4743808.
[19] Qi X, Li J, Deng H, et al. Neutrophil-to-lymphocyte ratio for the prognostic assessment of hepatocellular carcinoma: a systematic review and meta-analysis of observational studies. Oncotarget 2016;7:45283–301.
[20] Motomura T, Shirabe K, Mano Y, et al. Neutrophil-lymphocyte ratio reflects hepatocellular carcinoma recurrence after liver transplantation via inflammatory microenvironment. J Hepatol 2013;58:58–64.
[21] Hoffmann TK, Dworacki G, Tsukihiro T, et al. Spontaneous apoptosis of circulating T lymphocytes in patients with head and neck cancer and its clinical importance. Clin Cancer Res 2002;8:2553–62.
[22] Miyazaki S, Takasaki K, Yamamoto M, et al. Liver regeneration and restoration of liver function after partial hepatectomy: the relation of fibrosis of the liver parenchyma. Hepatogastroenterology 1999;46: 2919–24.
[23] Farges O, Malassagne B, Flejou JF, et al. Risk of major liver resection in patients with underlying chronic liver disease: a reappraisal. Ann Surg 1999;229:210–5.
[24] Vallet-Pichard A, Mallet V, Nalpas B, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and fibrotest. Hepatology 2007;46:32–6.
[25] Amorim TG, Staub GJ, Lazzarotto C, et al. Validation and comparison of simple noninvasive models for the prediction of liver fibrosis in chronic hepatitis C. Ann Hepatol 2012;11:855–61.
[26] Giannini EG, Testa R, Savarino V. Liver enzyme alteration: a guide for clinicians. CMAJ 2005;172:367–79.
[27] Okuda M, Li K, Beard MR, et al. Mitochondrial injury, oxidative stress, and antioxidant gene expression are induced by hepatitis C virus core protein. Gastroenterology 2002;122:366–75.
[28] Tarao K, Rino Y, Takemiya S, et al. Close association between high serum ALT and more rapid recurrence of hepatocellular carcinoma in hepatectomized patients with HCV-associated liver cirrhosis and hepatocellular carcinoma. Intervirology 2000;43:20–6.